Short Communication

Adult *Pseudomonas aeruginosa* Meningitis: High Incidence of Underlying Medical and/or Postneurosurgical Conditions and High Mortality Rate


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(Received June 25, 2007. Accepted August 15, 2007)

**SUMMARY:** We analyzed the clinical and laboratory characteristics, therapeutic outcome and prognostic factors of 25 cases of cerebrospinal fluid (CSF) culture-proven *Pseudomonas aeruginosa* adult bacterial meningitis (ABM). Twelve *P. aeruginosa* strains, isolated from clinical CSF specimens, were tested for antibiotic susceptibility. The 25 cases included 17 men and 8 women, aged 17 to 86 years (median = 51). Of the 25 cases of *P. aeruginosa* ABM, 18 were the result of postneurosurgical infection and the other 7 were spontaneous infections. The latter 7 cases had serious underlying medical conditions. The antibiotic susceptibility rates of the 12 strains were as follows: ceftriaxone 16.7% (2/12), ceftazidime 91.7% (11/12), cefepime 83.3% (10/12), imipenem 83.3% (10/12), meropenem 83.3% (10/12) and ciprofloxacin 66.7% (8/12). The therapeutic results showed an overall mortality rate of 40% (10/25). The emergence of third-generation cephalosporin-resistant *P. aeruginosa* strains cultured from clinical CSF specimens in recent years has resulted in a therapeutic challenge in the treatment of ABM.

In both eastern and western countries, *Pseudomonas aeruginosa* is not a common pathogen of bacterial meningitis (1,2). Although large-scale studies of overall adult bacterial meningitis (ABM) have been conducted (1,2), *P. aeruginosa* as a sole cause for ABM has been rarely examined in the literature. In this study, we analyzed the clinical and laboratory features and the therapeutic outcomes of 25 monomicrobial *P. aeruginosa* ABM cases. We also examined the antimicrobial susceptibility of 12 *P. aeruginosa* strains isolated from clinical cerebrospinal fluid (CSF) specimens.

During the study period (21 years, 1986 - 2006), 392 adult patients (≥17 years old) were determined to have culture-proven bacterial meningitis. Of these 392 cases, 350 had monomicrobial infections while the other 42 had polymicrobial infections. Of the 350 cases with monomicrobial infections, 29 cases had *Pseudomonas* ABM, and 25 of these 29 cases were cases of *P. aeruginosa* infection. The others were *Pseudomonas mendocina* (n = 2) and *Pseudomonas stutzeri* (n = 1), while one was not subtyped. Of the 42 cases of mixed infections, 12 involved *Pseudomonas* infection, and all 12 of these were *P. aeruginosa*. The criteria for a definite diagnosis of *P. aeruginosa* meningitis included the following: (i) a positive CSF culture of *P. aeruginosa*, (ii) clinical features of meningitis and (iii) purulent CSF features. The antibiotic susceptibility of the 12 isolated *P. aeruginosa* strains was tested using the Kirby-Bauer diffusion method (BBL, Muller-Hinton II agar; Becton Dickinson Microbiology Systems, Cockeysville, Md., USA) as described in the Clinical and Laboratory Standards (CLSI) guidelines for MICs. The antibiotics used in the susceptibility test included ceftriaxone, ceftazidime, cefepime, imipenem, meropenem and ciprofloxacin.

For comparative analysis, the 25 *P. aeruginosa* ABM cases were divided into two groups (fatal and non-fatal groups). Data including gender, type of acquisition of infection, type of infection, underlying conditions, clinical manifestations and therapeutic outcomes between these two patient groups were analyzed by means of a chi-square test or Fisher’s exact test. The age difference between the two patient groups was analyzed by means of Student’s t test. The consciousness levels of the two groups at the time of admission were analyzed by means of the Mann-Whitney test. CSF data for the leukocyte counts, glucose, total proteins and lactate concentrations were logarithmically transformed to improved normality, and comparisons were made using Student’s t test. All analysis was conducted using SAS (SAS Statistical Institute, Cary, N.C., USA).

The clinical and laboratory data of the 25 *P. aeruginosa* ABM cases are listed in Tables 1 and 2. The underlying conditions of the seven cases with spontaneous infection were systemic lupus erythematosus (SLE) (n = 1), otitis medium (n = 1), lung cancer with liver metastasis (n = 1), alcoholism with liver cirrhosis (n = 1), *P. aeruginosa* pneumonia with respiratory failure (n = 1), diabetes mellitus (DM) with end-stage renal disease (ESRD) (n = 1) and ESRD (n = 1). In the 18 cases with a preceding neurosurgical state, the median time lag between the last neurosurgical procedure and the diagnosis of *P. aeruginosa* ABM was 20 days (3 - 720 days). The CSF data, as shown in Table 1, revealed the features of purulent inflammation. The results of the antimicrobial susceptibility tests are listed in Table 3. Overall, 10 of the patients died and 15 survived, and only the difference in the level of the CSF leukocyte counts between the fatal and non-fatal groups was of statistical significance. Six of the 12 cases whose CSF-isolated *P. aeruginosa* strains were used in the antibiotic susceptibility test died. The major
antibiotics used for the treatment of these 12 cases were cefazidime for the six surviving cases, and cefazidime \( (n = 4) \), ceftazidime \( (n = 1) \) and meropenem \( (n = 1) \) for the other six expired cases.

This study revealed that *Pseudomonas* spp. accounted for 8.3% (29/350) of monomicrobial ABM and for 28.6% (12/42) of ABM with polymicrobial infection. Among the implicated *Pseudomonas* spp. of monomicrobial ABM, *P. aeruginosa* was the most common, accounting for 86.2% (25/29) of the cases. Of the 25 *P. aeruginosa* ABM cases, 72% (18/25) of the cases had a postneurosurgical state as the preceding event. In Taiwan, except for *Klebsiella pneumoniae* ABM, which is commonly seen in DM patients as a community-acquired, spontaneous infection (2,3), the high incidence of a postneurosurgical state as the preceding event is also common in other Gram-negative forms of ABM (2,4). Therefore, a positive culture result from the clinical specimens is the only practical method for further confirmation of *P. aeruginosa* ABM.

Table 1. Underlying medical conditions of the 25 adult *Pseudomonas aeruginosa* meningitis cases

<table>
<thead>
<tr>
<th>Non-fatal ( n = 15 )</th>
<th>Fatal ( n = 10 )</th>
<th>OR</th>
<th>95% CI</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at meningitis (y)</td>
<td>39.9±18.3</td>
<td>53.3±20.9</td>
<td>0.328</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>3</td>
<td>0.857</td>
<td>0.152-4.819</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical feature</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>11</td>
<td>8</td>
<td>0.917</td>
<td>0.123-6.825</td>
</tr>
<tr>
<td>Disturbed consciousness(^1)</td>
<td>11</td>
<td>8</td>
<td>0.688</td>
<td>0.1-4.719</td>
</tr>
<tr>
<td>Seizure</td>
<td>7</td>
<td>4</td>
<td>1.313</td>
<td>0.259-6.643</td>
</tr>
<tr>
<td>Septic shock</td>
<td>0(^2)</td>
<td>1</td>
<td>0.375</td>
<td>0.224-0.629</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>7</td>
<td>4</td>
<td>1.313</td>
<td>0.259-6.643</td>
</tr>
<tr>
<td>CSF leakage</td>
<td>0(^3)</td>
<td>1</td>
<td>0.375</td>
<td>0.224-0.629</td>
</tr>
<tr>
<td>Acquisition of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community acquired</td>
<td>5</td>
<td>3</td>
<td>1.167</td>
<td>0.208-6.559</td>
</tr>
<tr>
<td>Nosocomial acquired</td>
<td>10</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous meningitis</td>
<td>4</td>
<td>3</td>
<td>0.848</td>
<td>0.144-4.99</td>
</tr>
<tr>
<td>Postneurosurgical meningitis</td>
<td>11</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying medical disorders</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5</td>
<td>3</td>
<td>1.167</td>
<td>0.208-6.559</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>1</td>
<td>1</td>
<td>0.643</td>
<td>0.036-11.631</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>1</td>
<td>1</td>
<td>0.643</td>
<td>0.036-11.631</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1</td>
<td>2</td>
<td>0.286</td>
<td>0.022-3.669</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
<td>1</td>
<td>0.643</td>
<td>0.036-11.631</td>
</tr>
<tr>
<td>Peripheral blood study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis(^4)</td>
<td>11</td>
<td>8</td>
<td>0.688</td>
<td>0.1-4.719</td>
</tr>
<tr>
<td>CSF data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>2.53 (0.06-8.21)</td>
<td>0.60 (0.22-6.50)</td>
<td>0.403</td>
<td></td>
</tr>
<tr>
<td>Total protein (g/L)</td>
<td>1.61 (0.19-27.59)</td>
<td>3.80 (1.18-6.45)</td>
<td>0.295</td>
<td></td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>6.42 (0.22-21.70)</td>
<td>12.65 (2.79-23.43)</td>
<td>0.158</td>
<td></td>
</tr>
<tr>
<td>Leukocyte count (×10^6/L)</td>
<td>0.14 (0.003-15.8)</td>
<td>0.35 (0.29-3.78)</td>
<td>0.024</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Glasgow coma scale <15
\(^2\) Leukocyte count > 10^9/L.
\(^3\) Using a correction of 0.5 in every cell that contains a zero.

Table 2. Preceding neurosurgical events of the 18 adult *Pseudomonas aeruginosa* meningitis cases

| Traumatic skull fracture and subarachnoid hemorrhage (SAH) (1) | Traumatic skull fracture (1) | Traumatic subdural hemorrhage (SDH) + SAH + ventriculoperitoneal (VP) shunt (1) | Traumatic intracerebral hemorrhage (ICH) + SAH + SDH + craniectomy (1) | Traumatic epidural hemorrhage (EDH) + SDH + craniectomy (1) | Traumatic SDH + SAH + external ventricular drainage (EVD) (1) | Traumatic EDH + SDH + craniectomy (1) | s/p craniotomy (1) | Spontaneous ICH + EVD (1) | Arteriovenous malformation + ICH + VP shunt (1) | Aneurysm rupture + SAH + craniotomy + VP shunt (1) | Brain tumor + craniotomy + VP shunt (2) | Chiari malformation + craniectomy (1) | Nasopharyngeal carcinoma with skull base invasion (2) | s/p VP shunt (2) |
|---------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|-----------------------------|--------------------------------|
| Traumatic skull fracture and subarachnoid hemorrhage (SAH) (1) | Traumatic skull fracture (1) | Traumatic subdural hemorrhage (SDH) + SAH + ventriculoperitoneal (VP) shunt (1) | Traumatic intracerebral hemorrhage (ICH) + SAH + SDH + craniectomy (1) | Traumatic epidural hemorrhage (EDH) + SDH + craniectomy (1) | Traumatic SDH + SAH + external ventricular drainage (EVD) (1) | Traumatic EDH + SDH + craniectomy (1) | s/p craniotomy (1) | Spontaneous ICH + EVD (1) | Arteriovenous malformation + ICH + VP shunt (1) | Aneurysm rupture + SAH + craniotomy + VP shunt (1) | Brain tumor + craniotomy + VP shunt (2) | Chiari malformation + craniectomy (1) | Nasopharyngeal carcinoma with skull base invasion (2) | s/p VP shunt (2) |

Table 3. Results of antibiotic susceptibility tests of 12 *Pseudomonas aeruginosa* strains

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Susceptible test (MICs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>11</td>
</tr>
<tr>
<td>Cefepime</td>
<td>10</td>
</tr>
<tr>
<td>Imipenem</td>
<td>10</td>
</tr>
<tr>
<td>Meropenem</td>
<td>10</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>8</td>
</tr>
</tbody>
</table>

MICs, minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant.

(12/42) of ABM with polymicrobial infection. Among the implicated *Pseudomonas* spp. of monomicrobial ABM, *P. aeruginosa* was the most common, accounting for 86.2% (25/29) of the cases. Of the 25 *P. aeruginosa* ABM cases, 72% (18/25) of the cases had a postneurosurgical state as the preceding event. In Taiwan, except for *Klebsiella pneumoniae* ABM, which is commonly seen in DM patients as a community-acquired, spontaneous infection (2,3), the high incidence of a postneurosurgical state as the preceding event is also common in other Gram-negative forms of ABM (2,4). Therefore, a positive culture result from the clinical specimens is the only practical method for further confirmation of *P. aeruginosa* ABM.
The high incidence of third-generation cephalosporin-resistant Gram-negative pathogens isolated from CSF specimens of ABM was previously reported in our study in 1999 (5). In that study, Acinetobacter baumannii was found to be the most notorious pathogen, and the others were K. pneumoniae, Citrobacter freundii and Morganella morganii.

In the present study, the susceptibility rates of the tested P. aeruginosa strains to ceftriaxone, ceftazidime, cefepime, imipenem, meropenem and ciprofloxacin were 16.7% (2/12), 91.7% (11/12), 83.3% (10/12), 83.3% (10/12) and 66.7% (8/12), respectively. These data revealed that third-generation cephalosporin-resistant P. aeruginosa strains cultured from the clinical CSF specimens of ABM have emerged in recent years and were consistent with those reported by Lauderdale et al. (6) and Jones et al. (7). Although a judicious use of empiric antibiotic therapy is imperative in the treatment of serious infectious diseases in order to avoid the development of resistance to antimicrobial agents, the emergence of antibiotic-resistant, Gram-negative strains in clinical settings were significantly correlated with the increased consumption of antimicrobial agents (8,9). The emergence of clinical isolates of extended-spectrum cephalosporin-resistant Gram-negative bacteria, including P. aeruginosa strains, has resulted in a therapeutic challenge in the management of serious infectious diseases including nosocomial ABM (9,10). Although guidelines for the management of ABM have been reported (11,12), the presence of extended-spectrum cephalosporin-resistant P. aeruginosa strains should alert the clinicians who are dealing with the management of ABM. A more careful use of empiric antibiotics should be considered, especially in the cases of nosocomial ABM patients in a postneurosurgical state.

This study revealed a high mortality rate (40%, 10/25) for P. aeruginosa ABM. Among the clinical and laboratory factors, only the level of the CSF leukocyte count had prognostic significance. Actually, there are many factors that may influence the outcome of Gram-negative ABM (4), including early diagnosis based on a high level of clinical attentiveness, compliance with updated and evidence-based guidelines, and early and adequate antibiotic treatment based on the expected susceptibility and appropriate clinical microbiological advice. However, most of the P. aeruginosa ABM cases had complex preceding postneurosurgical conditions which may interfere with the analysis of the morbidity and mortality of ABM.

REFERENCES